IOHEXOL PLASMA CLEARANCE IN HEALTHY DOGS AND CATS

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Iohexol plasma clearance as a measure of glomerular filtration was determined in 31 dogs and 19 cats after an intravenous (IV) bolus injection. All animals were healthy and privately owned. Serial blood samples were taken before and up to 4 h after tracer injection. Iohexol plasma concentration was determined using X-ray fluorescence. A plasma tracer elimination curve was generated and clearance was calculated by dividing the injected dose by the area under the curve estimated using a two-compartment pharmacological model. Clearance was normalized to body weight (BW), body surface area (BSA), and extracellular fluid volume (ECFV). Mean, SD, and coefficient of variation of plasma clearance, before and after normalization, were calculated. Linear regression analyses were performed between body size and normalized plasma clearances. No significant linear relation was found between BSA and clearance normalized to BSA in dogs, and between BSA, BW, ECFV and clearance normalized to BSA, BW, and ECFV in cats. The optimal method for normalization of iohexol plasma clearance in dogs was by using BSA. In cats, all three methods tested were considered satisfactory. Normalization to BSA appears to be superior to normalization to BW and ECFV in dogs, and can be recommended for clinical use. *Veterinary Radiology & Ultrasound, Vol. 47, No. 2, 2006, pp 168–173.*

Key words: cat, dog, glomerular filtration rate, iohexol, plasma clearance.

Introduction

GLOMERULAR FILTRATION RATE (GFR) is the most reliable index of renal function.[1,2] Unfortunately, the reference method for GFR determination (i.e., renal clearance of inulin) is cumbersome, time consuming, and impractical in small animal medicine.[3] Over the last few years, there has been an increasing interest in veterinary medicine for alternative methods of GFR estimation, such as determination of plasma clearance of a tracer after a bolus intravenous (IV) injection.[4–9] Different tracers have been validated as alternatives to inulin, including creatinine, radioactive tracers, ^{99m}Tc-pentetate and ^{51}Cr-EDTA, and iodinated radiographic contrast media.[10–14] Radiographic contrast media are eliminated exclusively by glomerular filtration,[10] and radioactive compounds bound to iodine isotopes (^{125}I) have been used for GFR determination.[13,15,16] There has been a renewed interest for using radiographic contrast media for GFR determination with the introduction of nonradioactive methods, including X-ray fluorescence, for measuring iodine concentration in plasma.[11,17] Iohexol has been the most commonly used nonradioactive radiographic contrast medium, although other water soluble iodinated contrast media have similar pharmacologic properties and could also be used for GFR estimation.[10,18,19]

Although iohexol plasma clearance has been validated in dogs and cats as a measure of GFR,[6,20,21] its clinical use has been limited by lack of information regarding normal values. Most studies in small animals have used a limited number of conditioned animals of similar size,[6,20,22] which are not representative of the variability of size in a clinical population. In addition, normalization to body size has not been standardized fully in small animals and at least three methods have been proposed: by body weight (BW), by body surface area (BSA), and by extra cellular fluid volume (ECFV). Normalization to ECFV has been proposed because regulation of ECFV is closely related to regulation of glomerular filtration.[12,23,24] In humans, clearance values are usually normalized to BSA and reported as ml/min/m^2 or ml/min/1.73 m^2.[12] In dogs and cats, the most common method of normalization is by BW, but in a few recent studies clearance was normalized to BSA and ECFV.[7,25,26]

The purposes of this study were to validate iohexol concentration measured using an X-ray fluorescence technique and to determine the optimal method of normalization of iohexol plasma clearance in dogs and cats.

Material and Methods

Animals

Thirty-one privately owned adult healthy dogs and 19 cats of different breeds were selected for the study. Age of dogs ranged from 1 to 10 years (mean ± SD, 3.9 ± 3.1

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years) and age of cats ranged from 1 to 8 years (mean ± SD, 3.4 ± 2.5 years). Body weight ranged from 8.3 to 58 kg (mean ± SD, 25 ± 12.5 kg) for dogs and from 3 to 6.5 kg (mean ± SD, 4.2 ± 1.0 kg) for cats. A large number of dog breeds were represented, including Labrador Retriever (5), Beagle (5), Shepherd crossed (4), Siberian Husky (3), Fox Terrier (3), Beauceron (2), Border Collie, German Sherpherd Dog, Airedale Terrier, Leonberg, Old English Sheepdog, Rottweiler, Boxer, Great Dane, and Collie (1 each). Breeds of cats included domestic short hair (15), Persian (2), and Siamese (2). Only clinically healthy animals were selected, based on absence of history of clinical signs related to the urinary tract, unremarkable physical examination, and urine specific gravity, serum urea nitrogen and creatinine concentrations within normal range for our laboratory. In addition, all cats were euthyroid. All animals were well hydrated and were allowed to drink water ad libitum during the experiment.

Procedure

Catheters were placed in two peripheral veins and one heparinized blood sample (2 ml) was collected. One catheter was used for iohexol injection and the other for blood collection. Iohexol (Omnipaque 300®)* was used at a concentration of 300 mg of I/ml. The dosage of iohexol was 300 mg of I/kg (1 ml/kg) in dogs and 450 mg of I/kg (1.5 ml/kg) in cats. Iohexol was administered over a 30–60-s period. The catheter was flushed and removed. Time zero was defined as the end of injection. Ten heparinized blood samples (2 ml) were obtained at 5, 20, 40, 60, 80, 100, 120, 150, 180, and 240 min after injection. Animals were observed during the procedure for any adverse reaction to iohexol. Blood samples were centrifuged at 3000 g for 15 min; plasma was separated and then frozen at −30°C.

Iohexol Assay

Iodine concentration was measured in plasma by X-ray fluorescence technique (Oxford Lab-X-3000)†. The analyzer contained an anode in Palladium producing X-rays photoelectrically absorbed by iodine atoms resulting in characteristic X-rays emission specific for iodine. Characteristic X-rays were detected by a sodium iodine crystal confined in an inert gas (Argon). The analyzer was calibrated initially using a standard of lithium metaborate, from which the optimal conditions of the characteristic emission of iodine were established. Optimal tension was set at 10 kV and optimal intensity at 100 μA, with a measuring time of 200 s. The analyzer was tested with 1.5 ml standard solutions prepared from deionized water and iohexol containing 300 mg of I/ml at the dilution of 4000, 2000, 1000, 500, 400, 200, 100, 50, and 0 μg of I/ml. The standard 400 μg of I/ml was chosen as quality control (QC 400). Ten consecutive measures were performed with the QC 400, and mean, SD, and coefficient of variation were calculated. Before each series of analysis, the accuracy of the X-ray fluorescence measurement of iodine was checked with the QC 400 solution. The limit values for QC 400 measurement were set at 2 SD above and below the mean.

Iohexol Plasma Clearance

Iodine concentration found in the first sample, taken before the injection of the tracer, was subtracted from the iodine concentration of samples taken after the injection. A plasma tracer elimination curve was generated from the 10 data points. A two-compartment model was used, and the curve was fitted using a least-square method (Excel 98®)‡, to a double exponential function in the form of:

$$y = ae^{-\alpha t} + be^{-\beta t}$$

The area under the curve (AUC) was calculated from the integral of the above double exponential function between 0 and infinity[27]:

$$\mathrm{AUC} = a/\alpha + b/\beta$$

The iohexol clearance was calculated as the injected dose divided by AUC.[27,28] Clearance values were obtained in ml/min. Clearances were normalized using three methods: to the BW (expressed as ml/min/kg), to BSA (expressed as ml/min/m^2), and to ECFV (expressed as/min). BSA was calculated from BW using the general formula:[29]

$$\mathrm{BSA} = K \times (\mathrm{BW})^a/10^4$$

where BSA is expressed in m^2, BW in grams, K is a shape constant, and a is the mass exponent. The most commonly found values of K and a[29–32] were used in dogs and cats.

Volume of distribution of the two compartments, V_1 and V_2, was computed from the tracer elimination curve[28], and ECFV was calculated as $V_1 + V_2$.[10,28]

Statistical Analysis

Clearance values before and after normalization using BW, BSA, and ECFV of each dog and cat were recorded and mean ± SD of clearances were calculated for dogs and cats. The coefficient of variation (SD/mean) was determined and used to assess the usefulness of each normalization method. A linear regression analysis was performed between un-normalized clearance and BW and between normalized clearance and BW, BSA, and ECFV, respectively. The coefficient of determination (R^2) was computed. Significance was set at $P < 0.05$. Only methods of normalization with no significant influence of body size on nor-

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malized clearance by linear regression analysis were considered successful.

Results

A significant linear relation ($P = 1.000$) was found between the measured and known iodine concentrations in the standard solutions (Fig. 1). The regression line was not significantly different from the line of identity. Mean ($\pm$ SD) of repeated measures of the QC 400 was 406 ($\pm$ 8) with a coefficient of variation of 2%. The upper and lower limit of the QC measurement were set at 422 and 390 µg/ml, respectively. Quality control performed routinely before each set of measurement was always within this range.

No adverse reactions were observed during or after injection of iohexol. In dogs (Table 1), plasma clearance of iohexol ranged from 22.8 to 152 ml/min (mean $\pm$ SD, 69.0 ml/min $\pm$ 29.9) with a coefficient of variation of 43.4%. When normalized to BW, BSA, or ECFV, the coefficient of variation ranged from 18.6% to 22.8% (Table 1).

In dogs, a significant linear relation was found between un-normalized BW and clearance ($R^2 = 0.760$, $P < 0.0001$), between BW and clearance normalized to BW ($R^2 = 0.2625$, $P = 0.003$) (Fig. 2A), and between ECFV and clearance normalized to ECFV ($R^2 = 0.439$, $P < 0.0001$) (Fig. 2C). However, no significant linear relation was found between BSA ($K = 10.1$; $a = 0.66$) and clearance normalized to BSA ($R^2 = 0.096$, $P = 0.09$) or between BSA ($K = 10.1$; $a = 0.71$) and clearance normalized to BSA ($R^2 = 0.0413$, $P = 0.273$) (Fig. 2B).

In cats (Table 1), plasma clearance of iohexol ranged from 6.92 to 18.2 ml/min (mean $\pm$ SD, 11.3 ml/min $\pm$ 3.30) with a coefficient of variation of 29.3%. When normalized to BW, BSA, and ECFV, the coefficient of variation ranged from 23.5% to 26.8% (Table 1).

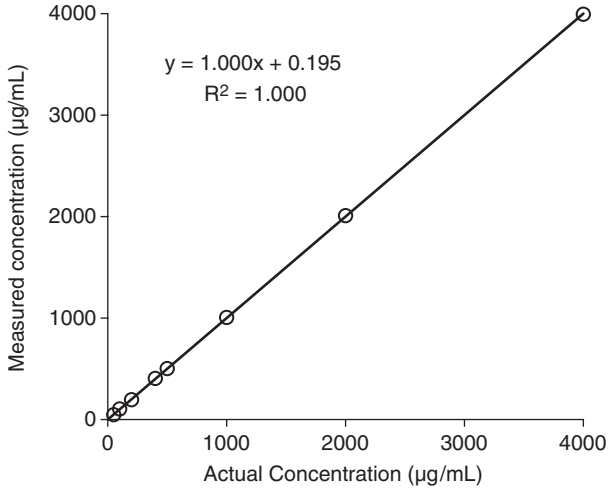

FIG. 1. Plot of known vs. measured iodine concentration using a prepared standard solution of iodine. The regression line is not significantly different from the line of identity.

TABLE 1. Iohexol Plasma Clearance Reference Values in 31 Dogs and 19 Cats

	Normalization	Unit	Mean	SD	CV (%)
Dogs	None	ml/min	69.0	29.9	43.4
	BW	ml/min/kg	2.91	0.60	20.6
	BSA ($K = 10.1$; $a = 0.66$)	ml/min/m^2	80.5	15.5	19.3
	BSA ($K = 10.1$; $a = 0.71$)	ml/min/m^2	70.3	13.1	18.6
	ECFV	/min	0.0145	0.0033	22.8
Cats	None	ml/min	11.3	3.30	29.3
	BW	ml/min/kg	2.75	0.74	26.8
	BSA ($K = 10.0$; $a = 0.66$)	ml/min/m^2	43.3	10.7	24.6
	BSA ($K = 10.6$; $a = 0.66$)	ml/min/m^2	41.2	10.1	24.6
	ECFV	/min	0.0132	0.0031	23.5

SD, standard deviation; CV, coefficient of variation: BW, body weight; BSA, body surface area; ECFV, extracellular fluid volume.

In cats, a significant linear relation was found between BW and unnormalized clearance ($R^2 = 0.382$, $P = 0.005$). However, no significant linear relation was found between BW and clearance normalized to BW ($R^2 = 0.076$, $P = 0.254$) (Fig. 3A), between BSA ($K = 10.6$ and 10.0; $a = 0.66$) and clearance normalized to BSA ($R^2 = 0.0002$, $P = 0.950$) (Fig. 3B), and between ECFV and clearance normalized to ECFV ($R^2 = 0.029$, $P = 0.487$) (Fig. 3C).

Discussion

Iohexol plasma clearance is slightly lower than ^{99m}Tc-pentetate clearance,[21,26] and slightly higher than exogenous creatinin clearance in dogs.[6] The results of this study are in agreement with the reference range of iohexol clearance reported in dogs and cats.[20,22,26,33] However, most previous studies have been performed on small samples of conditioned young animals of similar size, housed, and fed similarly, yielding a narrower range of clearance values[20,22,33] from which extrapolation to the canine and feline population presented to veterinary clinics may be questionable. Other studies on plasma clearance for estimation of GFR have used clinical patients with known or suspected renal disease.[4,21,25] Individuals selected for this study were healthy animals, with no evidence of urinary problems, of various breeds and ages, representative of the large spectrum of dogs and cats usually seen in clinics. Absence of renal disease was assessed by lack of relevant clinical signs, unremarkable physical examination, and normal results of routine serum biochemical renal profile and urinalysis. Additional more invasive tests, including renal biopsy or renal clearance of Inulin, would not have been acceptable for the owners. The procedure was performed on conscious, well-hydrated animals on an outpatient basis, as it would be for a prescribed procedure on a diseased patient. Although the number of healthy dogs and cats in the present study is greater than that in other previous similar studies, the effect of gender, age and breed could

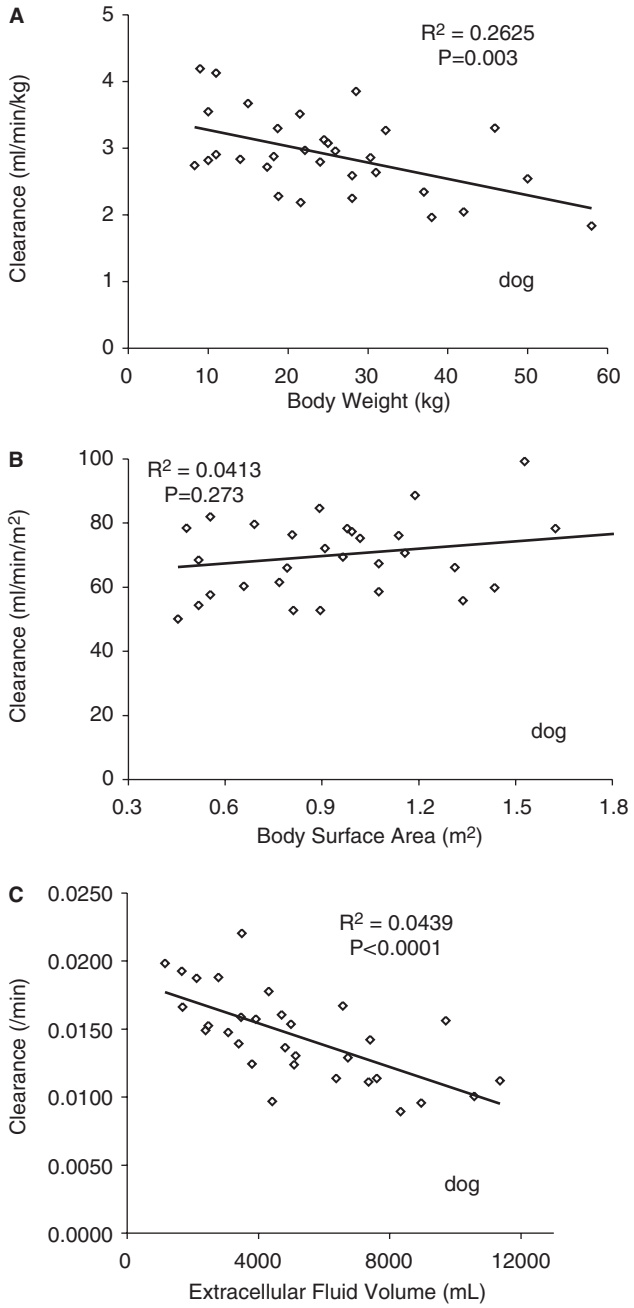

FIG. 2. Plot of normalized clearance against body weight (BW) (A), body surface area (BSA) ($K = 10.1$; $a = 0.71$) (B), and extracellular fluid volume (ECVF) (C) in 31 healthy dogs. Notice that normalization to body surface area (BSA) cancel the effect of body size on clearance value and that clearance normalized to body weight (BW) and extracellular fluid volume (ECFV) is still affected by body size.

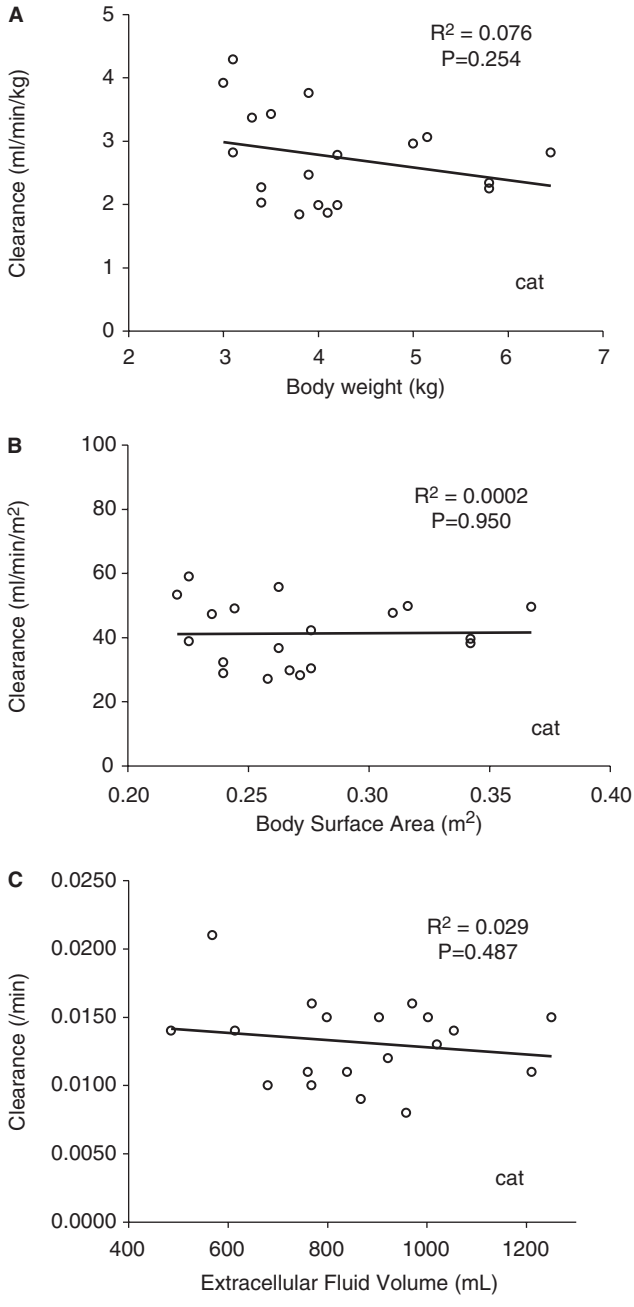

FIG. 3. Plot of normalized clearance against body weight (BW) (A), body surface area (BSA) ($K = 10.6$; $a = 2/3$) (B), and extracellular fluid volume (ECVF) (C) in 19 healthy cats. The three methods of normalization cancel the effect of body size on clearance value.

not be evaluated, because of the small size sample of each subpopulation. GFR has been shown to vary with gender and age in humans[12] and further studies specifically designed to evaluate the effects of these factors on iohexol plasma clearance would be needed in small animals.

A two-compartment pharmacokinetic model was chosen in the present study for the AUC calculation, because it describes accurately the distribution of contrast medium in the body.[10,28] Results of least-square fit in the present study support the use of this model when more than four samples are available.

No consensus has been reached, to date, regarding the optimal method of normalization of clearance values in dogs and cats.[25] Normalization to body size appears nec-

essary because of the great influence of body size on clearance reported as ml/min/animal, resulting in a large range of reference values and difficulties in interpretation.[34] A satisfactory method of normalization by body size would provide values independent of body size that can be compared with a normalized reference range. This was investigated in the present study by use of linear regression analysis between normalized clearance and body size. The ideal method of normalization would provide a flat (parallel to the *x*-axis) regression line. A satisfactory method of normalization would also narrow the spread of reference value above and below the mean by eliminating variation related to body size. This concept was translated to the present study by use of the coefficient of variation.

Clearance values of small animals have been most often normalized to BW, i.e., quoted as ml/min/kg, assuming a linear relation between clearance and BW.[7,26] One study, however, indicated that this relationship was nonlinear in very small and very large dogs.[34] Another study demonstrated a relation between BW and clearance normalized to BW, suggesting that normalization to BW was not satisfactory.[7] The results of this study confirm a persistent effect of body size on clearance normalized to BW in dogs.

In humans, clearance values, classically, have been normalized to BSA and reported as ml/min/m^2 or ml/min/1.73 m^2, corresponding to a "medium size" human.[12] This approach considers that BSA is more closely related with basal metabolic rate and kidney size than BW. In dogs and cats, few recent studies have reported clearance values normalized to the BSA [7,25,26] but none justified this approach other than with theoretical reasons and comparison with practice in humans. BSA can be estimated in dogs and cats from BW using the published formula[29] based on a general relation between BSA and BW in the form of $BSA = K \times BW^a$. The *K* constant, also known as the mass coefficient, varies with species and body conformation.[29] It is important to note that the proposed values of *K* for dogs and cats found in the literature were established from a limited number of individuals and therefore should not be considered universally valid.[29] The proposed *K* constant varied from 9.9 to 12.3 in dogs[29] and from 8.6 to 11.9 in cats.[32] The *a* constant, also known as the mass exponent, is supposed to be 2/3 for all species, based on the geometric relation between the surface area and the volume of an object.[29] However, it has been suggested that the value of 2/3 may not be accurate and the value of 0.71 has been proposed in dogs.[30] The results of this study support the use of normalization to BSA to express clearance in dogs. In cats, all three methods of normalization were satisfactory, most likely because of the smaller range of body size of cats as compared with dogs.

A third theoretical approach for normalization has been proposed, where clearance is normalized to ECFV.[10,24] The background basis advocated for normalization to ECFV is that regulation of ECFV is related closely to the regulation of glomerular filtration and GFR varies with ECFV under certain conditions.[24] In addition, normalization to ECFV abolishes differences between children and adults, as compared with normalization to BSA and BW.[35] ECFV can be calculated from the plasma elimination curve of the tracer and it can be demonstrated that the slope of the latter part of the plasma elimination curve drawn in a semi-log plot is a close approximation of clearance/ECFV.[10,23,24,35] This approach has been used in the dog, but its validity over other methods of normalization has not been tested.[23,36] The results of this study do not support normalization to ECFV in dogs because of a persistent significant effect of body size on clearance normalized to ECVF.

In summary, the wide range of iohexol plasma clearance in healthy dogs and cats justifies normalization of its value using body size for clinical use. In dogs, normalization by BSA can be recommended because it cancels the effect of body size on iohexol plasma clearance. Normalization by using BW and ECFV was not as effective, and a persistent dependence of body size and normalized clearance was found. In cats, the three methods of normalization could be used because they all cancel the effect of body size on normalized clearance.

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